VACCINE-INDUCED MASSIVE PULMONARY EMBOLISM AND THROMBOCYTOPENIA FOLLOWING A SINGLE DOSE OF JANSSEN AD26.COV2.S VACCINATION

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HIGHLIGHTS

• Thrombosis and thrombocytopenia after Sars-CoV-2 viral vector vaccine suggests VITT.

• Thrombosis in unusual sites (splenic, portal, mesenteric, adrenal) is typical of VITT.

• Anti-PF4antibody tests, if available, should be rapidly determined for diagnosis.

• IVIg could mask functional tests to confirm VITT diagnosis.

• Treatment with IVIg may be associated to false negative functional tests.

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KEYWORDS

COVID-19, Janssen, AD26.COV2.S, Vaccination, Vaccine-induced thrombosis with thrombocytopenia, pulmonary embolism

ABSTRACT

Vaccine-induced immune thrombotic thrombocytopenia (VITT) has emerged as a rare side effect of adenoviral vector-based vaccines against Coronavirus disease 2019 (COVID-19), and it is most frequently reported after Vaxzevria (AstraZeneca) vaccine. We described a case of severe thrombocytopenia associated with massive pulmonary embolism and portal vein thrombosis, occurring 13 days after the administration of the single dose adeno viral vector-based vaccine Ad26.COV2.S (Janssen vaccines, Leiden, Netherlands). Based on an early clinical suspect, the patient quickly received treatment with corticosteroids and intravenous immunoglobulins, followed by a rapid increase in platelet count that allowed full dose anticoagulation to be timely administered. Treatment with intravenous immunoglobulins, however, could mask the ability of anti-PF4-heparin antibodies to bind and activate platelets in the presence of heparin, leading to false negative results at the immunoassay functional test. Therefore, if VITT is suspected, blood samples for diagnostic confirmation should be collected prior to any treatment to improve diagnostic performance.

CASE REPORT

A 68-years-old man presented to the emergency department for left leg swelling with subacute pain, associated with weakness, dizziness and progressive dyspnoea. His medical history included hypertension and an euthyroid nodular goiter; personal history of thrombosis were negative. Molecular test for SARS-Cov2 nucleic acid (PCR) was negative and anti-spike IgG levels were 316 AU/ml. Vaccination for Coronavirus disease 2019 (COVID-19) with a single dose of Janssen Ad26.COV2.S vaccine (Janssen vaccines, Leiden, The Netherlands) was reported 13 days before. He denied any previous exposure to anticoagulants including heparins.

The patient was slightly dyspnoic and tachypnoic in room air with peripheral oxygen desaturation, his left leg was swollen and painful. The remaining examination was unremarkable. A point-of-care ultrasound evaluation revealed left femoro-popliteal deep vein thrombosis (DVT) and no signs of right heart overload/dysfunction. A total-body contrast-enhanced computed tomography-scan (CT-scan) showed massive bilateral pulmonary artery embolism and a right intra-hepatic portal thrombosis (Figure 1). Laboratory tests revealed severe thrombocytopenia (platelet count 7000/µl), markedly elevated levels of D-dimer (32533 ng/L), increase in serum lactate dehydrogenase (LDH) and C-reactive protein; values of fibrinogen, PT and aPTT were all within the normal range (Table).

Vaccine-induced immune thrombocytopenia (VITT) was suspected, therefore high-dose parenteral corticosteroids (methylprednisolone 80 mg IV daily) and intravenous immunoglobulins (1 g/kg/day for 2 days) were immediately started. An inferior caval vein filter (IVF) was implanted.

High titer antibodies to platelet factor 4 (PF4)–polyanion complexes were identified (optical density (OD) 2.21, negative <0.4) by enzyme-linked immunosorbent assay (ELISA Lifecodes PF4-Immucor-USA), whereas the rapid immunological chemiluminescence assay (HemosIL AcuStar HIT-IgG) was negative, in agreement with the known pattern of VITT-associated antiPF4-antibody positivity. The Heparin-induced platelet aggregation (HIPA) assay was also performed but it resulted negative. Serological tests for human immunodeficiency virus (HIV), hepatitis B and C viruses, TORCH screen, lupus-anticoagulant, anticardiolipin and anti β_2-glycoprotein antibodies were all negative. Blood levels of C and S proteins, C3 and C4 complement-fractions were within the normal range.

Reduced dose parenteral anticoagulation with fondaparinux was started at day 4, when platelet count reached 20000/mm^3 and direct oral anticoagulation was started at day 6 when platelet count exceeded 50000/mm^3. At day 16, a Doppler ultrasound showed recanalization of lower limb proximal veins, but IVF retrieval was postponed due to the presence of thrombosis of the caval vein filter. Patient was eventually discharged in good clinical conditions under direct anticoagulants; values of platelets, fibrinogen and LDH had returned in normal ranges.

We report a case of severe thrombocytopenia and venous thromboembolism occurring 13 days after administration of the single dose Janssen COVID-19 vaccine. To the best of our knowledge, this is the first case of VITT associated to the Ad26.COV2.S vaccine described in Italy.

On April 4th, 2021, the European Medicines Agency safety Committee provided a systematic assessment of thromboembolic events associated with thrombocytopenia following the administration of the ChAdOx1 nCoV-19 viral vector-based vaccine (Vaxzevria, AstraZeneca, University of Oxford, and Serum Institute of India). A total of 169 cases of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis were reported to EudraVigilance, leading to the conclusion that a causal relationship between vaccination with Vaxzevria and thromboembolic events with thrombocytopenia was at least a reasonable possibility. Later, given that 6 cases of CVST with thrombocytopenia were also identified in the United States among recipients of approximately 7 million doses of Janssen vaccine, the U.S. Food and Drug Administration and the Centers for Disease Control and Prevention suggested temporary pausing of the administration of Janssen vaccine to allow further investigation [1].

VITT has been mainly reported among females aged <55 years old and between 4 and 16 days after receiving adenoviral vector-based vaccines, although exceptions exist, such as cases observed in males, in subjects up to 77 years old, and occurring as early as 2 to late 28 days after vaccination [Gresele, 2021a]. Its pathogenesis is still unclear and under investigation, but many reports highlight similarities with autoimmune heparin-induced thrombocytopenia (HIT), tracking a continuum between different platelet-activating anti-PF4/heparin disorders. Autoimmune HIT is a form of HIT without any previous exposure to heparin. A possible role of the adenoviral vector platform and/or of free nucleic acids in the development of the autoimmune response have been suggested [Gresele, 2021a]. *Mc Gonagle* et al. suggested that the local tissue micro-trauma following vaccine inoculation brings adenoviral DNA in contact with platelet-factor 4 (PF4), thus increasing anti-PF4 autoantibody production in susceptible subjects [Mc Gonagle, 2021]. Other hypotheses related the syndrome to the adenoviral vector platform carrying a message from a RNA virus with the consequent random splicing of the DNA message producing unwanted circulating soluble spike protein [Gresele, 2021a].

Venous thrombosis in VITT typically occurs in unusual sites, including cerebral, splanchnic (splenic, portal, mesenteric, adrenal), and ophthalmic veins. Anticoagulation is a cornerstone of HIT-related thrombosis but is prevented by severe thrombocytopenia and DIC. Full-dose anticoagulants should be administered as soon as possible in VITT patients, provided that concurrent thrombocytopenia is corrected [Gresele, 2021b]. To this end IVIg administration, or in severe/refractory cases plasma exchange, are critical to interrupt the immune-mediated mechanisms causing VITT and to obtain a fast increase in platelet count that, in turn, allows full dose anticoagulants to be safely administered in a timely manner [Gresele, 2021b]. In our patient a fast satisfactory response to high-dose corticosteroids and IVIg treatment was obtained in terms of platelet counts allowing full dose anticoagulation to be applied with resolution of the acute clinical picture. Even if there is paucity of data about optimal anticoagulant treatment of VITT, principles of guidance are based on the use of non-heparin-based anticoagulants (e.g. fondaparinux, argatroban), and to switch to direct oral anticoagulants when the platelet count reaches 50000/mm^3 [2]. Two positive assays are conventionally required to confirm a suspected VITT: a quantitative ELISA assay, which detects and quantifies antiPF4 antibodies, and a functional assay, which assesses the ability of anti-PF4-heparin antibodies to bind and activate platelets in the presence of heparin. However, the simultaneous administration of IVIg could mask their functional ability to activate platelets [Bourguignon, 2021]. This might also be of importance because if VITT is suspected, as it was in our case, blood samples for diagnostic confirmation should be collected prior to any treatment to improve diagnostic performance. When treatment has to be started as soon as possible and immunoassay tests are not rapidly available, d-dimer levels may guide the clinical management [Zazzeron, 2021].

Many questions related to VITT remain unsolved: first, what are the viral-vector vaccine components responsible of VITT. Second, what are the molecular mechanisms behind the heterogeneity of results of anti-PF4 functional assays. Third, if is it possible to screen for populations susceptible to VITT and last if vaccinated people with VITT develop more severe symptoms after SARS-CoV-2 re-exposure. Further studies are needed to solve these important and urgent questions.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Laboratory Characteristics of the Index Patient.

Laboratory Analysis	Reference Value	Day 1	Day 4	Discharge
Hemoglobin (g/dl)	13.5 – 18.0	12.2	10.2	11.3
Platelet count (per mm3)	140000 – 440000	7000	24000	230000
Leukocytes (per mm3)	4.500 – 10.800	6.350	5.540	8.420
Partial thromboplastin time (sec)	22 - 32	25	28	22
International normalized ratio	0.85 – 1.20	1.08	1.33	1.05
Thrombin time (sec)	70 - 120	86	61	91
Fibrinogen (mg/dl)	160 - 420	217	58	350
D-dimer (mg/liter)	0 – 350	32533	ND	ND
Aspartate aminotransferase (U/liter)	0 - 41	46	33	16
Alanine aminotransferase (U/liter)	3 - 63	60	56	32
γ-Glutamyltransferase (U/liter)	0 - 55	108	112	ND
Lactate dehydrogenase (U/liter)	0 - 248	302	195	ND
C-reactive protein (mg/dl)	0 – 0.8	5.5	ND	ND